exists between efficacy (cough suppression) and safety (side-effects), and further investigation of patients' priorities should be considered. Developing more selective $P2X_3$ receptor antagonists might provide similar or better anti-tussive efficacy with fewer side-effects.

Nevertheless, if approved by the US Food and Drug Administration or the European Medicines Agency, gefapixant would be the first medicine approved specifically to help these patients. The success of gefapixant is contributing to a change in the management of chronic cough, providing desperately needed relief for patients affected by chronic cough and a treatment option for clinicians.

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Waning of COVID-19 vaccine effectiveness: individual and public health risk

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High coverage rates of vaccination against COVID-19 are envisaged to end the pandemic. However, waning of vaccine-induced protection is a growing concern that has been fostered by data on vaccine effectiveness against the currently circulating omicron SARS-CoV-2 variant of concern (VOC).

A systematic review and meta-regression by Daniel R Feikin and colleagues[1] in *The Lancet* provides robust evidence of waning vaccine effectiveness over time. The authors identified 18 studies matching their inclusion criteria, of which three were randomised controlled trials (RCTs). Studies with participants of any age were included in the main analysis, with nine of 18 studies also including adolescents (aged ≥12 years). Information on sex or ethnicity distribution per study was not provided. Evidence from the meta-regression suggested a decrease in protection against SARS-CoV-2 infection by 21·0% (95% CI 13·9–29·8; on the basis of evidence from six studies) over a 6-month period from full vaccination across all ages and for all investigated vaccine types (Pfizer–BioNTech Comirnaty, Moderna-mRNA-1273, Janssen-Ad26.COV2.S, and AstraZeneca-Vaxzevria). Vaccine effectiveness against severe disease decreased by 10·0% (95% CI 6·1–15·4; on the basis of evidence from five studies); however, vaccine effectiveness against severe disease remained higher than 70% for 6 months. Subgroup analysis of studies with older adults (as defined per study, but with a minimum age of 50 years) showed no statistically significant difference when compared with analyses of all ages. Variant-specific time analysis supported that reduced vaccine effectiveness does not only relate to alternating effectiveness against specific variants, but that waning immunity is probable. The authors[1] raised concerns about the serious risk of bias caused by confounding of several non-RCTs that were included. Primary data were adjusted for incomplete and different sets of covariates across studies, and considerable heterogeneity was detected. The pooled analysis might therefore be considered controversial, and the magnitude

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of estimated effects should be interpreted with caution. Nevertheless, all but one of the identified studies (a phase 3 RCT on mRNA-1273 with completed follow-up of the masked phase, median 5·3 months, before the emergence of VOCs)[2] reported waning vaccine effectiveness over time.

The findings of Feikin and colleagues[1] relate to the effect of waning immunity after full vaccination, without booster doses. Furthermore, they are restricted to evidence before the emergence of omicron.[1] A report on population-based surveillance data from the UK illustrated waning of protection against symptomatic disease after two-dose and three-dose vaccination schedules, which was also observed when infections by the omicron variant began.[3] The decline of protection in the UK was more distinctive for omicron than for delta. With an mRNA-based booster dose (Pfizer-BNT162b2 or mRNA-1273), vaccine effectiveness against omicron reached more than 60% 2 weeks after the booster dose. Approximately 4 months after the booster, a decline in protection was noted. Similar to the findings of Feikin and colleagues, a reduction in vaccine effectiveness against severe disease (ie, hospitalisation) was observed after full vaccination; however, this reduction was less great than that observed after symptomatic infection. The protective effect against hospitalisation after omicron infection could be restored up to 90% with an mRNA vaccine booster; a decrease to 75% 3–4 months after the booster was noted.[3] US data from a test-negative study design support high vaccine effectiveness against omicron-related hospital admission after three doses (89%, 95% CI 84–92).[4]

The need for repeated booster vaccination is widely discussed, with some countries starting to offer a fourth dose. Preliminary data from Israel suggest an increased protective effect against infection (risk reduced by a factor of 2·0, 95% CI 2·0–2·1) and severe illness (risk reduced by a factor of 4·3, 2·4–7·6) 12 or more days after dose four when compared with people who received three doses.[5] Optimal vaccination strategies are being sought, and heterologous vaccination schedules, optimal time interval between doses, or variant-adapted vaccines are being discussed.[6] The overall aim of vaccination against COVID-19 is to prevent severe disease and deaths. The prevention of severe disease is strongly related to the maintenance of a functioning health-care system, and thus combines the individual and public health risk of the COVID-19 pandemic.[7] Therefore, the goal of public health measures is also to limit the spread of the virus and to interrupt transmission chains. Vaccination also has an effect on transmission rates; however the magnitude of effect changed in the light of arising VOCs.[8] A study from Denmark investigated household transmissions of the omicron and delta variant.[9] The secondary attack rate was approximately 10% lower in households with fully vaccinated primary delta cases and 20% lower in households with booster-vaccinated primary delta cases, when compared with unvaccinated primary cases. Although a vaccine-induced reduction of transmission under omicron was also observed (but to a lesser extent), the findings underline that the continuing emergence of new VOCs poses a threat to reducing the spread of SARS-CoV-2.[10] Without sufficient vaccine coverage and equitable access to booster vaccination, waning of vaccine effectiveness represents both an individual and public health risk.

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Prophylaxis with anti-activated factor XII for hereditary angioedema

Thomas Barwick/Getty Images

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Hereditary angioedema is a rare autosomal dominant genetic disorder characterised by recurrent, localised swellings in various tissues including the skin, genitals, abdomen, face, and oropharyngeal region. These attacks can be painful, debilitating, and life-threatening, substantially affecting quality of life.[1,2] Inadequate control of the contact system, consisting of factor XII (FXII), plasma kallikrein, and high molecular weight kininogen, results in excessive bradykinin formation, which increases vascular permeability and thus causes angioedema attacks.[3]

In the 1960s, the first therapies for hereditary angioedema were introduced: attenuated androgens and antifibrinolytics.[4] They became widely used for both acute treatment and long-term prophylaxis of angioedema attacks, but are becoming less favoured due to frequent side-effects, low efficacy, and the availability of better management options.[5] The discovery of C1-inhibitor deficiency as the cause of angioedema in patients with hereditary angioedema and subsequent attempts to use purified C1-inhibitor concentrate as treatment led to the development of commercial plasma-derived C1-inhibitor concentrates. In the past two decades, bradykinin B2 receptor antagonists and prekallikrein and kallikrein inhibitors have been clinically investigated,[6] leading to the US Food and Drug Administration approval of icatibant, ecallantide, lanadelumab, and berotralstat.[3] These therapies have improved the lives of patients with hereditary angioedema, but many still have side-effects and breakthrough attacks.[7]

Meanwhile, mutations in FXII, among other things known from its role in the contact system, were found to be associated with a rare form of hereditary angioedema with normal C1-inhibitor (HAE-nC1-INH) in 2006.[8] This knowledge helped the development of garadacimab, a first-in-class, fully human, recombinant monoclonal antibody targeting activated factor XII (FXIIa). In *The Lancet,* Timothy Craig and colleagues[9] report findings from a randomised, placebo-controlled, phase 2 study investigating garadacimab in 32 patients with hereditary angioedema from 12 centres in four countries. Patients with hereditary angioedema with C1-inhibitor deficiency (HAE-C1-INH; median 39·5 years [IQR 28·0–52·5]; 18 [56%] of 32 patients were female and 14 [34%] were male) were randomly assigned to placebo or 75 mg, 200 mg, or 600 mg garadacimab every 4 weeks for 12 weeks. The primary outcome was the time-normalised number of attacks per month. The researchers found that subcutaneous administration of 200 mg and 600 mg garadacimab every 4 weeks significantly reduced the attack rate compared with placebo (median reduction of 100% with 200 mg [p=0·0002], and 93% with 600 mg [p=0·0003]), and in post-hoc analyses 75 mg garadacimab also significantly reduced the attack rate compared with placebo (median reduction of 100% [p=0·0002]). Garadacimab was well tolerated and seven (88%) of eight patients randomly assigned to the 200 mg group did not experience any attacks during the treatment period.

The most common adverse events associated with garadacimab treatment were injection-site reactions. No evidence of anti-drug antibodies was found and prolongation of the activated partial thromboplastin time was only seen in the 600 mg group. However, this group did not have any haemorrhagic events, in line with observations in patients who are FXII deficient who do not experience a bleeding tendency.[10]